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Maternal anti-HLA class I antibodies are associated with reduced birth weight in thrombocytopenic neonates

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ABSTRACT

In this comparative cross-sectional study, possible associations between maternal anti-HLA class I antibodies and birth weight in neonatal thrombocytopenia are explored. Although commonly detected in pregnancies and generally regarded as harmless, it has been suggested that such antibodies might be associated with fetal and neonatal alloimmune thrombocytopenia (FNAIT). As a link between FNAIT due to human platelet antigen 1a-specific antibodies and reduced birth weight in boys has previously been demonstrated, we wanted to explore whether maternal anti-HLA class I antibodies might also affect birth weight. To examine this, suspected cases of FNAIT referred to the Norwegian National Unit for Platelet Immunology during the period 1998–2009 were identified. Pregnancies where the only finding was maternal anti-HLA class I antibodies were included. An unselected group of pregnant women participating in a prospective study investigating maternal–fetal hemodynamics at the University Hospital North Norway during the years 2006–2010 served as controls. Twenty-nine percent of controls had anti-HLA class I antibodies. The thrombocytopenic neonates had a significantly lower adjusted birth weight (linear regression, $P = 0.036$) and significantly higher odds of being small for gestational age (OR = 6.72, $P < 0.001$) compared with controls. Increasing anti-HLA class I antibody levels in the mother were significantly associated with lower birth weight and placental weight among thrombocytopenic neonates, but not among controls. These results indicate that maternal anti-HLA class I antibodies in thrombocytopenic neonates are associated with reduced fetal growth. Further studies are needed to test if placental function is affected.

1. Introduction

How a semi-allogenic fetus manages to survive pregnancy is still quite an enigma. It is, however, clear that the maternal immune system recognizes and responds to fetal antigens (Arck and Hecher, 2013).

The human leukocyte antigen class I (HLA class I) antigens are present on all nucleated cells and platelets in the human body. The genes that encode HLA class I antigens are the most polymorphic in the human genome. Exposure to incompatible HLA antigens can activate the host immune system and lead to the production of alloantibodies. It is well known that anti-HLA class I antibodies can have severe clinical consequences, such as the rejection of allografts (Lee et al., 2002; Zhang et al., 2005) or the destruction of transfused platelets (Novotny, 1999).

Maternal anti-HLA class I antibodies are commonly detected during pregnancy (approximately 30% of pregnant women) (Morin-Papunen et al., 1984; Regan et al., 1991; King et al., 1996; Masson et al., 2013). In the context of pregnancy, these antibodies are generally considered harmless. Reports have described an association between maternal anti-HLA class I antibodies and recurrent miscarriage (Sargent et al., 1988; Nielsen et al., 2010). Possible associations between maternal anti-HLA class I antibodies and placental abruption (Steinborn et al., 2004) and preeclampsia (Buurma et al., 2012) have also been suggested. However, there are few systematic studies on anti-HLA class I antibodies and pregnancy complications (Lashley et al., 2013).

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Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal alloantibodies targeting human platelet antigens (HPAs) on fetal platelets, most commonly HPA-1a (Davoren et al., 2004; Skogen et al., 2010). FNAIT occurs at a frequency of about 1.5 per 1000 births (Dreyfus et al., 1997; Kjeldsen-Kragh et al., 2007). Intracranial hemorrhage (ICH) is the most severe complication and is reported in around 10% of patients with severe FNAIT (Mueller-Eckhardt et al., 1989; Kamphuis et al., 2010). Numerous reports describe suspected cases of FNAIT with maternal anti-HLA class I antibodies as the only finding and a possible explanation of neonatal thrombocytopenia (Saito et al., 2003; Moncharmont et al., 2004; Thude et al., 2006; Gramatges et al., 2009; Starcevic et al., 2010). It has therefore been suggested that maternal anti-HLA class I antibodies might cause FNAIT.

We have previously demonstrated an association between maternal antibodies against HPA-1a and reduced birth weight in boys (Tiller et al., 2012). The aim of this study was to explore whether there are similar associations between maternal anti-HLA class I antibodies and birth weight in relation to neonatal thrombocytopenia.

2. Methods

2.1. Study population

The two study groups (cases and controls) were identified and selected from pregnant populations that were originally either clinical referrals to the Norwegian National Unit for Platelet Immunology or participants in a different study (Flo et al., 2010, 2014). We performed a secondary analysis of these data using a comparative cross-sectional study design. Selection of the study population is presented as a flow chart in Fig. 1.

All pregnancies referred to the Norwegian National Unit for Platelet Immunology in Tromsø, Norway, for suspected FNAIT during the period 1998–2009 were identified. Pregnancies were included as cases if maternal anti-HLA class I antibodies were detected and neonatal thrombocytopenia was confirmed. Pregnancies were excluded if platelet-specific (anti-HPA-) antibodies were detected or if other reasons for neonatal thrombocytopenia were found. Information regarding demographic characteristics, obstetric history, course, and outcome of pregnancy was obtained from the medical records. All maternal blood samples were taken postpartum.

Of 82 mothers who fulfilled the inclusion criteria, 62 consented to participate. There was one twin pregnancy. Thirteen neonates were further excluded from analysis: eight for other possible reasons for neonatal thrombocytopenia (two with congenital cytomegalovirus infections, one with Jacobsen's syndrome, one with maternal immune thrombocytopenic purpura, one with neonatal hemochromatosis, one with Noonan's syndrome, one with Down's syndrome, one case of neonatal death 18 days after birth, where the autopsy showed underdeveloped bone marrow), and five cases where maternal sera were unavailable for antibody analysis. Thus, data from 50 cases over a period of 11 years were included for further analysis.

An unselected population of pregnant women originally included in a prospective study investigating maternal-fetal hemodynamics at the University Hospital of Northern Norway during the period 2006–2010 served as controls (Flo et al., 2010, 2014). Maternal blood samples were taken at 22–24 weeks of gestation. Additional maternal blood samples acquired within three days of delivery were available for seven controls. All samples were tested for the presence of maternal anti-HLA class I antibodies and categorized as either anti-HLA class I antibody-negative or -positive. Of 250 pregnancies in the control group, 72 (29%) tested positive for maternal anti-HLA class I antibodies. Platelet counts were obtained from 45 randomly selected neonates in the control group, none of which was thrombocytopenic.

All pregnancies were dated based on ultrasonography performed in the second trimester. Preeclampsia was diagnosed according to current ISSHP criteria (Tranquilli et al., 2014).

2.2. Definitions

Small for gestational age (SGA) was defined as birth weight less than the 10th percentile for gestational age based on singleton percentile curves (Skjaerven et al., 2000).

Infants born before 37 + 0 gestational weeks were defined as premature.

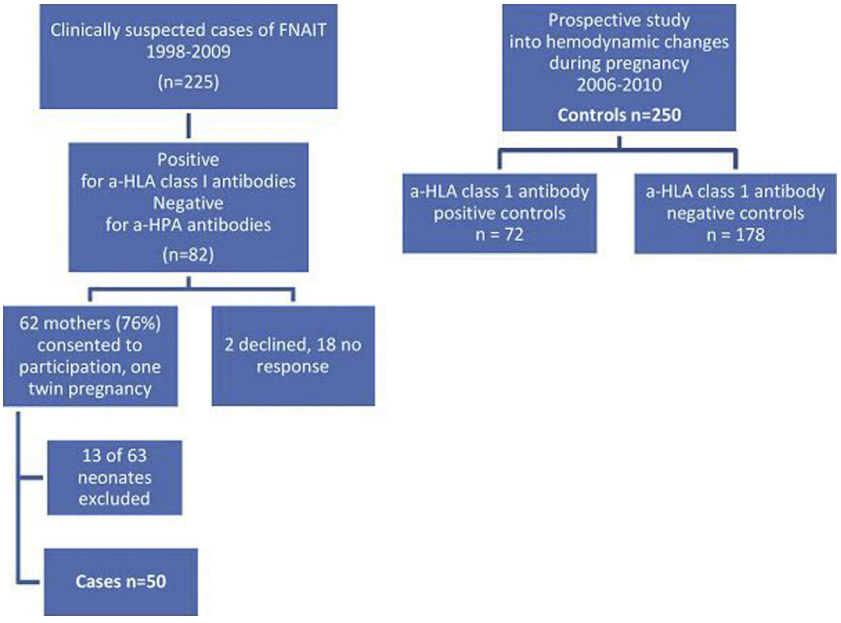

Fig.1. Cases consisted of pregnancies where the mother was anti-HLA class I antibody-positive and the neonate had suspected FNAIT, while controls consisted of normal pregnancies.